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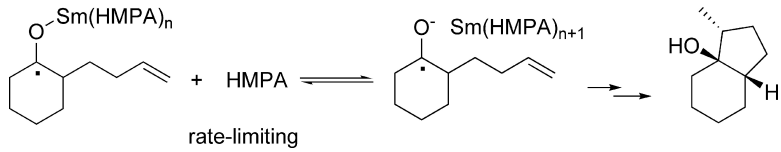

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Mechanistic Study of Samarium Diiodide-HMPA Initiated 5-*exo*-*trig* Ketyl−Olefin Coupling: The Role of HMPA in Post-Electron Transfer Steps

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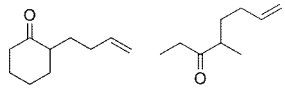
One of the most important follow-up steps in the reduction of ketones by samarium diiodide (SmI_2) is addition of a ketyl radical to an olefin. Intramolecular ketyl−olefin and related coupling events provide routes to a range of important intermediates[1] and are critical in a number of tandem bond-forming events initiated by SmI_2.[2] Proton donors and hexamethylphosphoramide (HMPA) are oftentimes vital components in these and related reactions, but their mechanistic role is poorly understood. To elucidate the mechanistic role of these additives, a series of proton donors in the presence of HMPA were examined to study their impact on the rate and mechanism of ketyl−olefin coupling. The data described herein show two important features: (1) HMPA plays an important mechanistic role in ketyl−olefin coupling after the initial reduction of a ketone through the formation of a solvent-separated ion pair from the metal-coordinated ketyl intermediate, and (2) in the presence of HMPA, proton donors do not play a mechanistic role in the rate-determining step of the reaction.

Although the mechanism of SmI_2-initiated ketyl−olefin coupling has not been investigated in detail, the seminal studies of Curran[3] and Molander[2h] have probed the mechanistic aspects of this reaction through careful product studies and other experimental observations. Curran proposed that ketone reduction by SmI_2 is a relatively fast, reversible process with the equilibrium lying to the side of unreacted ketone and SmI_2.[3] This hypothesis was based on the observation that reactions between ketones and SmI_2 to produce diols are relatively slow, while ketones containing an appropriately placed pendant olefin are reduced and subsequently cyclize at a faster rate. In a series of elegant product studies, Molander proposed that the sterically encumbered SmI_2−HMPA reductant was responsible for the observed products and diastereoselectivities of 5- and 6-exo ketyl−olefin cyclizations.[2h]

To analyze the hypotheses of Molander and Curran, detailed studies were performed to elucidate the mechanistic role of HMPA and three proton donors (methanol, trifluoroethanol, and 2-methyl-2-propanol) in the reductive coupling of 2-but-3-enylcyclohexan-1-one (**1**) and 4-methyloct-7-en-3-one (**2**) shown below. A series



1 **2**

of rate experiments were initiated, and the rate orders for each component of the reaction were determined. Rate studies were performed under pseudo-first-order conditions with substrate in excess by monitoring the decay of the Sm absorption at 555 nm. In all cases, the rate order of proton donors was zero in the presence of HMPA and product studies showed that they had no impact on the diastereoselectivity of the reaction. The k_{obs} and rate order data for all other reaction components are contained in Table 1. The rate order of 1 for HMPA was surprising since previous studies on the reduction of dialkyl ketones provided a rate order of 0 for HMPA.[4] Examination of parent ketones 3-pentanone and cyclohexanone under the conditions employed for the rate studies of **1** and **2** confirmed these findings (Supporting Information). To further explore the impact of HMPA on the cyclization process, the reaction rate for the reduction of **1** and **2** was monitored over a broad concentration range, as shown graphically in Figure 1. In the absence of HMPA, the reaction rate is on the order of the natural decay of SmI_2 under the conditions of our study. After addition of at least 4 equiv of HMPA, the rate was accelerated substantially. A subsequent increase in the rate was observed as the concentration of HMPA was increased, and the rate of the reaction did not begin to level off until addition of a large excess. The data obtained from this experiment are consistent with saturation behavior.

Table 1. Rate Orders for Substrate, SmI_2, and HMPA

		rate order		
system	$k_{obs}(s^{-1})$[a]	substrate[b]	SmI_2[c]	HMPA[d]
1	$6.0 \pm 0.1 \times 10^{-1}$	1.0 ± 0.1	1.0 ± 0.1	1.08 ± 0.03
2	$3.9 \pm 0.1 \times 10^{-2}$	0.9 ± 0.1	1.0 ± 0.1	1.0 ± 0.1

[a] $[SmI_2] = 5$ mM, HMPA = 40 mM, [substrate] = 60 mM, [ROH] = 125 mM. [b] $[SmI_2] = 5$ mM, HMPA = 40 mM, [substrate] = 50−90 mM, [*t*-BuOH] = 125 mM. [c] From ref 4. [d] $[SmI_2] = 5$ mM, HMPA = 10−240 mM, [substrate] = 60 mM, [*t*-BuOH] = 125 mM.

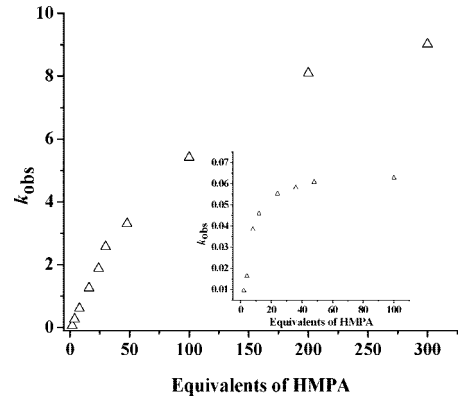


Figure 1. Equivalents of HMPA versus k_{obs} for reduction of **1**. The inset shows equivalents of HMPA versus k_{obs} for reduction of **2**. $[SmI_2] = 5$ mM.

Elegant studies by Daasbjerg and Skrydstrup have shown that addition of 4−10 equiv of HMPA produces $[Sm(THF)_2(HMPA)_4]I_2$, and further addition beyond 10 equiv likely produces $[Sm(HMPA)_6]I_2$ through the equilibrium shown in Scheme 1.[5] A

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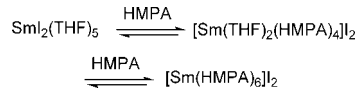
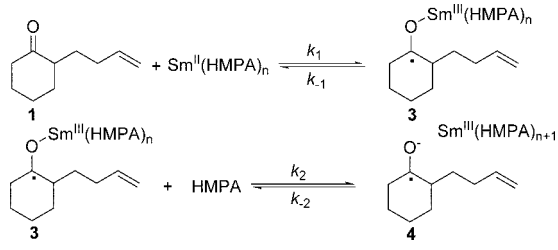
Scheme 1



further consequence of HMPA coordination to Sm(II) is the production of a more powerful reductant.[6] Taken together, these studies are consistent with HMPA playing an important role in accelerating the rate of reactions and providing increased stereoselectivity through the formation of a sterically encumbered reductant.[1,4] Recently, Hoz has provided evidence that HMPA plays a mechanistic role in the reduction of diaryl ketones after initial reduction to the ketyl radical anion.[7] In Hoz's study, HMPA was shown to slow the rate of bimolecular coupling through complexation of Sm(III) required to bridge two colligating radical anions. Although the present work shows that HMPA accelerates ketyl−olefin cyclization beyond concentrations required to increase the reducing power of SmI_2, the question remains whether the additive could be mechanistically important in a post-electron transfer step.

To elucidate the mechanistic role of HMPA, it is important to keep a number of points in mind: (1) The formation of the Sm−HMPA complex is required for initiation of ketyl−olefin cyclization. (2) Addition of successive amounts of HMPA to SmI_2 in THF likely drives the equilibrium shown in Scheme 1 to the saturated Sm(II)−HMPA complex while simultaneously increasing the polarity of the solvent milieu. (3) The rate law describing the reaction provides the stoichiometry of the activated complex relative to the reactants.[8] (4) Since the ketyl−olefin cyclization is fast, it is reasonable to assume that the rate-limiting step of the reaction occurs before the cyclization event.[9]

Scheme 2



On the basis of our experimental findings and the points described above, a mechanism is proposed as shown in Scheme 2. Coordination of HMPA to Sm(II) enables reduction of the ketone to produce a ketyl radical. Coordination of the intermediate ketyl to the sterically congested Sm(III)HMPA stabilizes the intermediate but also inhibits cyclization.[2h] Liberation of the contact ion pair through displacement by an equivalent of HMPA leads to solvent-separated ion pair **4** releasing the steric constraint to cyclization. The different saturation maxima for **1** and **2** (Figure 1) may be due to ease of displacement from Sm(III) by HMPA.

Application of a steady-state approximation to the concentration of ketyl radical **3** provides the expression shown in eq 1, which predicts that the system should display saturation kinetic behavior with respect to [HMPA].[10]

$$\frac{d[SmI_2]}{dt} = \frac{k_1 k_2 [Sm(HMPA)_n][HMPA][\mathbf{1}]}{k_{-1} + k_2[HMPA]} \quad (1)$$

When $k_{-1} \gg k_2$, the equation simplifies to that shown in eq 2:

$$\frac{d[SmI_2]}{dt} = k_{obs}[Sm(HMPA)_n][HMPA][\mathbf{1}] \quad (2)$$

indicating that the rate will exhibit a first-order dependence on [SmI_2], [substrate], and [HMPA]. At modest concentrations of HMPA, these conditions are met for both substrates examined in this study.

The results described herein are consistent with a broader role for HMPA beyond production of a more powerful, sterically crowded Sm(II) reductant in 5-*exo-trig* ketyl−olefin cyclizations. The mechanism derived from rate studies shows that HMPA is important not only in increasing the reduction potential of the Sm(II) reductant but also in enhancing the inherent reactivity of the radical anion through conversion of a sterically congested contact ion pair to a solvent-separated ion pair, allowing cyclization to occur. The absence of an influence on the stereoselectivity and rate expression by proton donors is consistent with proton transfer occurring after the rate and stereoselection steps, suggesting that the ability of HMPA to coordinate strongly to Sm prevents coordination of proton donors to the inner-sphere, distancing them from the vicinity of the reacting centers. The mechanistic complexity of the SmI_2−HMPA-initiated ketyl−olefin cyclization shows that simple empirical models based on structural knowledge of ground-state reductants are likely to contain a high degree of uncertainty.

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Supporting Information Available: General experimental methods, spectroscopic and rate data. This material is available free of charge via the Internet at http://pubs.acs.org.

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